AMENDMENTS TO THE CLAIMS

Claims 1-27 (Cancelled)

Claim 28 (Currently Amended): An isolated DNA molecule which comprises an expression system for the production of a calcium ion channel α_1 subunit protein which expression system comprises

a nucleotide sequence encoding a functional T-type, low voltage activated calcium channel α_1 subunit or the complement to said encoding nucleotide sequence, wherein said encoding nucleotide sequence comprises

~~(a)~~ a nucleotide sequence encoding the amino acid sequence encoded by SEQ. ID. NO: 18~~; or~~

~~(b) the complement of a nucleotide sequence that hybridizes under conditions of medium hybridization stringency to the nucleotide sequence of (a)~~.

Claims 29-34 (Cancelled)

Claim 35 (New) Recombinant host cells which are modified to contain the DNA molecule of claim 28.

Claim 36 (New): A method for producing a functional T-type calcium ion channel α_1 subunit protein which method comprises culturing the cells of claim 35 under conditions wherein said expression system produces said protein.

Claim 37 (New): A method for preparing cells which produce a functional T-type calcium ion channel α_1 subunit protein which method comprises introducing into said cells the DNA molecule of claim 28.

Claim 38 (New): An isolated DNA molecule which comprises an expression system for production of a calcium ion channel α_1 subunit protein fragment, which expression system comprises a nucleotide sequence encoding a T-type low voltage activated calcium channel α_1 subunit fragment or the complement to said encoding nucleotide sequence, wherein said encoding nucleotide sequence consists of the nucleotide sequence encoding the amino acid sequence encoded by SEQ. ID. NO: 18.

Claim 39 (New): Recombinant host cells which are modified to contain the DNA molecule of claim 38.

Claim 40 (New): A method for producing a functional T-type calcium ion channel α_1 subunit protein which method comprises culturing the cells of claim 39 under conditions wherein said expression system produces said protein.

Claim 41 (New): A method for preparing cells which produce a functional T-type calcium ion channel α_1 subunit protein which method comprises introducing into said cells the DNA molecule of claim 38.

REMARKS

Claims 28-34 were pending, of which claims 28-33 were subject to appeal as the Office withdrew claim 34 from consideration. An RCE is submitted herewith, which reopens prosecution and withdraws the application from appeal pursuant to MPEP § 1215.01. Claims 29 to 34 are cancelled herein without prejudice or disclaimer, claim 28 is amended and claims 35 to 41 are new. Support for the amendments to claim 28 and new claims 35 to 41 is in the specification and claims as originally filed. No new matter has been introduced and entry of the above amendments and new claims is respectfully requested.

The applicants submitted on March 18, 2003 a Supplemental Information Disclosure Statement, consideration of which is respectfully requested.

Summary

With the deletion of hybridization language in part (b) of claim 28, the rejection under 35 U.S.C. § 112, second paragraph is moot. The remaining rejections are for alleged lack of utility and alleged lack of a written description.

The applicants respectfully assert that there is no *prima facie* showing that the claimed subject matter lacks utility. As explained hereafter, the calcium ion channel α_1 subunit protein alone is useful in assays for screening compounds that can treat diseases such as epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, and Lambert- Eaton Syndrome (*see e.g.,* specification at page 9, lines 7-10). The applicants have utilized a nucleic acid specified by claim 28 in a screening assay and have identified several compounds that inhibit the encoded functional calcium channel α_1 subunit. The applicants expect that compounds identified by the screening assay are useful for treating one or more of the above-identified diseases. Accordingly, the claimed subject matter has a substantial, specific and credible utility as described in greater detail hereafter.

The claimed subject matter also is fully supported by a written description in the specification. As explained hereafter, the nucleotide sequence of SEQ ID NO: 18 represents approximately 85% of a full-length α_1 subunit, and the remaining 15% is from known T-type

receptor α_1 subunits. A person of ordinary skill in the art understood the disclosure of SEQ ID NO: 18 in the specification inherently provided a description of the entire coding sequence for the α_1 subunit because the full-length nucleotide sequence could be elucidated without performing any additional recombinant procedures. Accordingly, the specification provides a full written description for the claimed subject matter.

The Rejection Under 35 U.S.C. § 112, Second Paragraph is Moot

Amended claim 28 no longer includes the subject matter of subpart (b), which was directed to a complement of the nucleotide sequence that hybridizes under conditions of medium hybridization stringency to the nucleotide sequence of (a). The rejection is moot because it pertained only to this deleted language.

The Claimed Subject Matter has Utility

The specification clearly describes utility for the recombinant materials claimed. It is to provide recombinant α_1 subunits which can be used in an assay system to identify compounds which would be useful in treating specifically enumerated diseases including epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma and Lambert-Eton Syndrome (*e.g.*, see specification at page 9, lines 7-10.) This portion of the specification provides a nexus for screening assays the applicants have developed using the nucleic acid of claim 28. The applicants expressed the claimed nucleic acid in cells and utilized the cells to screen a library of compounds for those that modulated the activity of the encoded α_1 subunit. Using these assays, the applicants have identified a number of modulatory compounds. It is expected that compounds identified by the assays are useful for treating one or more of the diseases referenced in the specification. The applicants can provide the Office with declaratory evidence of these screening assays should the Office require. It is noted that the nucleic acid of claim 38 is useful for detecting an interaction between a compound and the encoded α_1 subunit fragment even though the fragment is not functional.

There is a specific, substantial and credible utility for the nucleic acids of claims 28 and 38 because the encoded α_1 subunits are useful for identifying compounds that interact with the encoded subunits. The utility provided by the assays is specific because the assays identify discrete

compounds that interact with the encoded subunit and may be useful for treating one or more diseases referenced in the specification. The assays also belly a substantial utility as they represent a real-world use of the claimed nucleic acid. The assays also represent a well-established substantial utility as persons of ordinary skill in the art routinely utilize calcium channel assays to identify compounds useful for treating diseases associated with aberrations in calcium channels. The assays also have a credible utility as they successfully have been utilized to identify compounds which modulate the activity of the encoded α_1 subunit. Accordingly, the claimed subject matter is supported by a specific, substantial and credible utility.

There is no reasoning or evidence present in the record for doubting applicants' characterization of the utility or to provide a *prima facie* case that the utility is insubstantial, non-specific or not credible. The Office has simply asserted without basis that the asserted utility does not meet the required criteria. The Office appears to require *in vivo* data showing the compounds are useful for treating the referenced diseases to establish a utility. It should be noted, however, that the screening assay itself is a specific, substantial and credible utility and that absolute certainty the identified compounds will successfully treat a disease is not required. *In re Brana*, 34 USPQ.2d 1436 (Fed. Cir. 1995).

Applicants also request notice be taken of U.S. patents 6,309,858 and 6,358,706 (Exhibits F and G), which are presumed valid. The utilities of α_1 subunits of T-type calcium channels are described in substantially the same way in the specifications of these patents as the description herein. In the '706 patent, at column 16, beginning at line 11, the same approach as described herein is set forth. The nature of the diseases that can be treated by the compounds identified are set forth in column 17, beginning at line 17. It is not seen that the nature of the description in the '706 patent differs materially from that herein. Similarly, in the '858 patent, the α_1 subunit is used to screen for modulators as set forth in column 2, lines 53-63 and column 18, line 17-column 19, line 63. The use of the compounds identified is set forth in a manner similar to that set forth in the present specification in column 19, lines 63-66.

The Office stated that it would not consider the utility of the present application in view of the '858 and '706 patents as each patent application is examined on its own merits. It is respectfully submitted, however, that the Office should be applying uniform standards of examination to each and every patent application and the utility established in the present application should be assessed

in view of the utility present in the present '858 and '706 patents. It would be concluded that the present application provides the requisite utility if the Office conducts itself properly and performs such an analysis.

In addition, Exhibit B clearly establishes that compounds selective for T-type channels would be useful pharmacologically. For example, on page 347, it is stated

> Although to date there are no highly selective T-type channel blockers, studies using a variety of compounds that all have activity against these channels have led to the conclusion that selective blockers might be useful in regulating proliferation, blood pressure and abnormal neuron firing. T-type channels may play a central role in thalamic dysrhythmias and therefore blockers may be useful not only against epilepsy, but also a wide spectrum of neurological disorders.

It is precisely for the purpose of discovering such selective T-type blockers that the claimed materials are useful. No reason can be comprehended by applicants as to why their descriptions of utility are considered inadequate. Accordingly, reversal of the rejection grounded in lack of utility is respectfully requested.

The Claimed Subject Matter Finds a Written Description in the Specification

As noted above, the specification provides a full written description for the claimed subject matter as it is clear a person of ordinary skill in the art would understand the applicants had possession of a nucleic acid which encoded the full amino acid sequence of an α_1 subunit. The nucleotide sequence of SEQ ID NO: 18 represents 85% of the α_1 subunit. The remaining 15% was known to the person of ordinary skill in the art because it was an already-identified portion of another well-known T-type calcium channel α_1 subunit. As noted in the declaration submitted herewith as Exhibit A, a person of ordinary skill in the art could readily complete the α_1 subunit nucleotide sequence of SEQ ID NO: 18 without performing a further experiment. As there is no requirement for an *ipsis verbis* description of the claimed subject matter, it is sufficient to show that the person of ordinary skill in the art understood the applicants had possession of the claimed subject matter and consequently disclosed a full written description.

The basis for a written description in the applicants' Appeal Brief filed February 24, 2003 is incorporated herein by reference and certain portions of the basis is included hereafter for the

convenience of the Office. First, it is unclear whether the Office disputes the statements made in the specification that the α_1 subunit of the T-type channel, displayed alone, provides functional calcium ion channel activity. The application clearly states that calcium ion channel activity is exhibited by the α_1 subunit taken alone. Page 3, lines 19-20, state that the α_1 subunit is the major pore forming subunit and contains a voltage sensor and binding sites for calcium channel antagonists. Page 5, lines 15-17, state that the α_1 subunit alone can form functional calcium channels, which additional subunits may at best modulate. Example 2 (that describes assessing calcium ion channel activity) states that the α_1 calcium channel cDNA may be transfected alone into cells for performing such assessment as well as in combination (page 18, lines 9-10; page 19, lines 11-12). Applicants have found nothing in the record either of evidence or of reasoning that would cause the reader to doubt these statements. Absent such reasoning or evidence, these statements must be accepted. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

Clearly in contention, however, is whether the disclosure of a nucleotide sequence encoding 85% of the full-length channel provides a sufficient description of the functional channel to place this channel in the art, and to convey to the skilled artisan that the applicants were in possession of recombinant materials that encode functional T-type α_1 subunits. Applicants have submitted sworn testimony providing evidence that disclosure of the nucleotide sequence encoding 85% of the full-length α1 subunit demonstrates possession of recombinant materials for production of a functional calcium ion channel. There is no dispute that if the protein containing only the sequence translated were produced, this would not itself be functional. However, there is no requirement that a written description be set forth in *haec verba* in the application in order to be considered adequate. See, for example, Kenn*ecott Corp. v. Kyocera Int'l, Inc.*, 835 F.2d 1419, 5 USPQ.2d 1194 (Fed. Cir. 1987). In that case, claims to ceramics with an equiaxed structure were considered supported in the parent application which failed to mention this characteristic. The characteristic was considered inherent in the description provided of the material itself.

Similarly, here, the description of the essential portion missing 15% of the amino acid sequence (domain IV) is inherent in the description of the 85% set forth in the application.

It may be helpful to provide some background information on the known structural features of voltage-gated ion channels. A rough illustration of the disposition of these channels in the cell membrane is shown on page 1 of Exhibit C. As shown, the α_1 subunit is the major feature of the

channel which contains the pore-forming unit as well as a voltage sensor. In high voltage channels, the α_1 subunit is associated with a β subunit which is intracellular (the T-type channels lack association with β) and with an $\alpha_2\delta$ subunit, a major portion of which is extracellular. A γ subunit may also span the membrane in association with the $\alpha 1$ subunit.

Exhibit C, page 2, shows a schematic of the $\alpha 1$ subunit in more detail. Starting at the N-terminus, which is internal to the cell, there are four domains, I-IV, homologous to each other, each of which contains six transmembrane segments, including the illustrated S4 region that acts as a voltage sensor and a P-loop or pore region that contains the amino acid residues responsible for ion selectivity. Domains II and III are separated by a large intracellular loop which has additional functions not relevant here. The 85% of the amino acid sequence set forth in the specification extends past the complete domain III as shown in the figure. The missing portion is only a portion of domain IV.

This was explained under oath by one of the applicants, Dr. Terrance Snutch, who is a recognized practitioner in this field. As Dr. Snutch explains, in paragraph 8 of his declaration (Exhibit A), the explicitly disclosed sequence SEQ ID NO: 18 starts at the N-terminus and encodes three complete homologous structural domains, I, II and III up to a transmembrane segment of domain IV that precedes the pore region of domain IV. As Dr. Snutch testified, it is well known that structural domains II, III and IV result from the evolutionary duplication of domain I (see also Exhibit B, page 339, right column). Therefore, the remaining sequence in structural domain IV will be functional if it is simply a replication of the already disclosed sequence of domain III. One of ordinary skill would have no difficulty in "filling in the blanks" of the *in haec verba* described sequence since the necessary verbiage is inherent in the 85% of the sequence already disclosed. And as described in the declaration in Exhibit A, the remaining 15% of the nucleic acid sequence was provided without the requirement of performing further experiments. Thus, the specification established possession of the full α_1 subunit sequence without requiring any experimentation.

Respectfully, to require an *in haec verba* description of sufficient sequence to represent a functional α_1 subunit puts form over substance. The ordinary practitioner would require no experimentation in order to provide a nucleotide sequence encoding a functional calcium ion channel. The nature of the omitted 15% is simply inherent in the description of the 85% described, when put in context of the further description that this represents a calcium ion channel whose

evolutionary history is well understood in the art. It would be equivalent to stating that a written description is inadequate if a word is omitted from a sentence when the reader would automatically know that it was there. Is the sentence, "The sun rises the morning" an inadequate non-enabling written description because "in" is missing between "rises" and "the"? There should be 23 letters in the sentence and there are only 21. Therefore, 10% of the letters are missing. But could anyone possibly fail to understand what the other two letters have to be? They are inherent in the sentence as presented.

The Office argued further experimentation was required to arrive at the nucleotide sequence of claim 28. As explained above, this position is not tenable because the nearly complete sequence of SEQ ID NO: 18 provided full possession of the nucleotide sequence of claim 28. And there is no question that the specification provides complete possession of the nucleotide sequence in claim 38.

The Office also asserted that the declaration in Exhibit A would not be considered because the declarant Terrence Snutch was an interested party. It is respectfully submitted that this standard is improper because the declaration provides factual evidence, not opinion. That the remaining 15% of the sequence is present in α_1 subunits disclosed in the art is a matter of fact rather than opinion. Accordingly, this factual evidence must be considered by the Office irrespective of the delcarant's interest.

Applicants further call the attention of the Office to U.S. patent 5,710,250 (Exhibit D). This patent contains claims to a "substantially pure α_2 subunit of a human calcium channel encoded by DNA comprising a sequence of nucleotides that encodes the α_2 subunit of a human calcium channel." The structural characteristics of the coding nucleotide sequence are defined in the claims as the ability to hybridize under conditions of high stringency with a "naturally occurring complementary DNA encoding a human calcium channel subunit" that includes "all or a portion of the nucleotide sequence set forth in Figures 2a-2f and the portion includes at least nucleotides 43-272" of those figures. Figures 2a-2f do not encode a human α_2 subunit, they encode a rat skeletal muscle α_2 subunit. The actual nucleotide sequence encoding a human α_2 subunit is set forth in Figures 3a-3d and is marvelously incomplete. It comprises only 1,849 nucleotides out of an expected 7,000-8,000.

The claims of the '250 patent are presumed valid under 35 U.S.C. § 282, and applicants thereby are entitled to assume that a claim to a "functional" α_2 subunit of a calcium ion channel can

validly issue based on the disclosure as a written description of the actual human nucleotide sequence corresponding to less than half of its full-length, a proportion that is clearly not itself functional. If that assumption is true, then it seems more than reasonable that a description *in haec verba* of 85% of the relevant full-length sequence would be adequate to support a claim to recombinant materials encoding a functional channel.

Furthermore, even the full-length α_2 subunit claimed in the '250 patent, taken alone, is not "functional" - there is no description in the patent which even asserts functionality of the α_2 subunit taken alone; indeed, it is now known that the α_2 subunit is actually associated with further amino acid sequence and comprises an $\alpha_2\delta$ subunit as shown on page 1 of Exhibit C. As described in Exhibit E, the $\alpha_2\delta$ subunit does not function alone, but rather modulates the calcium ion channel activity of the α_1 subunit. As stated, for example, in the Abstract, "Coexpression of $\alpha_2\delta$-3 with α_{1C} and cardiac β_{2A} or α_{1E} and β_3 subunits shifted the voltage dependence of the channel activation and inactivation in a hyperpolarizing direction and accelerated the kinetics of current inactivation. There is no description of $\alpha_2\delta$ subunits functioning alone; they require the presence of α_1 in order to function.

For the reasons set forth above, applicants request that the Office recognize that an adequate written description of the claimed subject matter has been provided.

CONCLUSIONS

The amendments to the claims render moot the rejection under 35 U.S.C. § 112, second paragraph. The claimed subject matter has a well-known specific, substantial and credible utility as the nucleic acids are utilized in assays for screening compounds that should be useful for treating diseases discussed in this specification. The specification also provides a written description for the claimed subject matter as the person of ordinary skill in the art understood the applicants had possession of an α_1 subunit nucleotide sequence at the time of filing. Accordingly, it is respectfully requested that the Office withdraw the rejections to the claimed subject matter and issue a notice of allowance.

In light of the above amendments and remarks, applicants believe that the claims continue to be in condition for allowance and urge passage of the application to issue. The Office is invited to contact applicants' agent at the number listed below if it would be helpful in any way to resolve remaining issues

In the event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 381092000700. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 30, 2003

Respectfully submitted,

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